ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA
www.scielo.cl

Andes pediatr. 2024;95(5):573-582
DOI: 10.32641/andespediatr.v95i5.5047

ORIGINAL ARTICLE

Prolonged treatment of patent ductus arteriosus with paracetamol in very low birth weight preterm infants

Tratamiento prolongado del ductus arterioso persistente con paracetamol en recién nacidos prematuros de muy bajo peso

Scarlet Cotua Silva[a,b], **Aldo Bancalari Molina**[a,b], **Macarena Sandoval Seguel**[a,b]

[a]Servicio de Neonatología, Hospital Guillermo Grant Benavente. Concepción, Chile.
[b]Departamento de Pediatría, Facultad de Medicina, Universidad de Concepción. Concepción, Chile.

Received: November 24, 2023; Approved: Jun 3, 2024

What do we know about the subject matter of this study?

In recent years, the indication for paracetamol for patent ductus arteriosus closure has increased due to its lower adverse effects compared with ibuprofen and indomethacin. However, the dose and duration of treatment are still under study.

What does this study contribute to what is already known?

This is the first study to evaluate treatment with intravenous paracetamol for 6 consecutive days in preterm newborns less than 1500 g with hemodynamically significant patent ductus arteriosus (hs-PDA). It is shown that prolonged administration of paracetamol does not increase the rate of primary ductal closure with respect to the usual duration of treatment for 3 days.

Abstract

Hemodynamically significant patent ductus arteriosus (hs-PDA) in very low birth weight (VLBW) infants continues to be an issue of research regarding the timing of treatment and which would be the most appropriate drug. **Objective:** To assess the outcome of prolonged treatment with paracetamol in the closure of hemodynamically significant patent ductus arteriosus in preterm newborns. **Patients and Method:** Retrospective study in VLBW infants with echocardiographic and clinical diagnosis of hs-PDA who received treatment with intravenous paracetamol at 15 mg/kg every 6 hours for 6 days. At the end of treatment, control echocardiography was performed. To evaluate possible side effects, biochemical tests were performed before and after treatment. **Results:** 62 VLBW infants with average weight and gestational age ± SD of 1,094 ± 257 g and 27,9 ± 2,1 weeks, respectively, were evaluated. At the beginning of the treatment, the mean ± SD ductal size was 2,2 ± 0,5mm. The ductal closure rate with the first cycle of treatment was 69.4% (43/62) and with the second cycle, it increased to 87,1% (54/62). Surgical closure was required in 9,7% of the neonates (6/62). An increase in the incidence of retinopathy of prematurity and acute kidney injury was observed in preterm infants whose

Keywords:
Patent Ductus Arteriosus;
Paracetamol;
Acetaminophen;
Newborn;
Premature

Correspondence:
Scarlet Cotua Silva
sacs1506@gmail.com

Edited by:
Patricia Mena Nannig

How to cite this article: Andes pediatr. 2024;95(5):573-582. DOI: 10.32641/andespediatr.v95i5.5047

hs-PDA did not close with the first cycle of paracetamol. Biochemical tests after the treatment showed a significant decrease in creatinine and an increase in platelet count ($p < 0,05$). **Conclusion:** In VLBW infants with hs-PDA, prolonged treatment with intravenous paracetamol does not increase the ductal closure rate compared with the usual 3-day treatment.

Introduction

Patent ductus arteriosus (PDA) is one of the most frequent complications in very low birth weight preterm newborns, increasing its incidence to more than 50% in preterm newborns with birth weight less than 1,000 g[1-4].

Hemodynamically significant PDA (hs-PDA) is associated with some morbidities such as pulmonary hemorrhage, pulmonary edema, and heart failure[5]. In addition, left-to-right shunting of PDA results in systemic hypoperfusion that may be associated with renal failure and necrotizing enterocolitis (NEC)[5].

Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and ibuprofen have been used for pharmacological closure of hs-PDA, achieving effective closure by reducing prostaglandin synthesis, but with some systemic complications such as peripheral vasoconstriction, gastrointestinal bleeding and perforation, decreased platelet aggregation, hyperbilirubinemia, and renal failure[6-8]. Therefore, the use of paracetamol both orally and intravenously has been explored[9,10].

Paracetamol inhibits the activity of the enzyme prostaglandin synthetase, which reduces prostaglandin synthesis[9]. Unlike indomethacin and ibuprofen, its therapeutic action does not produce systemic vasoconstriction, which reduces possible systemic adverse effects. Therefore, it was initially used in patients with elevated bilirubin and serum creatinine levels in whom the use of NSAIDs was contraindicated[8,11].

A recent Cochrane review, which included 8 studies comparing the efficacy and safety of paracetamol with indomethacin, ibuprofen, and placebo concluded that paracetamol has similar efficacy to indomethacin and ibuprofen with fewer renal and hepatic side effects[12].

The dose of paracetamol for hs-PDA closure varies according to different studies[13]. Recent studies have shown a high closure rate and/or significant decrease in PDA caliber, by oral or intravenous administration of paracetamol[9,10,14,15].

In a previous study in our service, intravenous paracetamol was used for 3 days, with a closure percentage of 66.7%, with no side effects observed (unpublished observations). In order to increase ductal closure in our population of premature newborns and given that no collateral effects were observed, the possibility of doubling the treatment with intravenous paracetamol was considered, to increase the percentage of ductal closure.

This study hypothesized that doubling the number of days and dose of paracetamol treatment will increase the rate of primary ductal closure, without increasing adverse effects.

The objective of the study was to evaluate the outcome of prolonged treatment with paracetamol in the closure of hs-PDA in preterm newborns.

Patients and Method

Retrospective descriptive study on treatment with paracetamol for hs-PDA closure in very low birth weight (VLBW) preterm newborns with echocardiographic and clinical diagnosis of hs-PDA performed within the first week of postnatal age. The study was conducted on VLBW preterm newborns hospitalized in the Neonatal Intensive Care Unit of the *Hospital Guillermo Grant Benavente* of Concepción, Chile, between July 1, 2019, and June 30, 2022 (3 years).

Inclusion criteria comprise preterm newborns ≤ 32 weeks and/or with birth weight less than 1500 g, clinical and ultrasound diagnosis of hs-PDA, and VLBWNB treated with paracetamol before 7 days postnatal life and exclusion criteria were newborns with congenital heart disease or major malformations, incomplete laboratory test data in the clinical record, and newborns who died before 7 days of life.

The diagnosis of hs-PDA was made by echocardiography performed by a pediatric cardiologist, with a portable 2D color Doppler ultrasound (Vivid-i, GE Healthcare, USA), within the first week of postnatal life, and was followed up at the end of treatment. The dose of paracetamol used was 15 mg/kg every 6 hours (60 mg/kg/day) for a 6-day consecutive period, corresponding to one course of treatment (intravenous paracetamol, Fresenius Kabi-Chile laboratory, solution for infusion 10 mg/ml). The drug was administered intravenously for a period longer than 60 minutes. When the treatment failed, a new course of paracetamol was administered at the same dose and duration.

The criteria proposed by P. McNamara and A. Sehgal, which include clinical and echocardiograph-

ic signs, were adapted for the diagnosis of hs-PDA[16] and used as a protocol of the service. The echocardiographic criteria for defining hs-PDA were ductal diameter ≥ 1.5 mm, ductal diameter larger than that of the left pulmonary artery (LPA) measured in right parasternal short axis; dilatation of left cavities or left atrial-to-aortic ratio (LA/Ao) > 1.5, measured in left parasternal long axis; decreased or absent diastolic flow in superior mesenteric artery, middle cerebral artery, or renal artery, in addition to clinical parameters such as continuous left infraclavicular murmur; signs of systemic hypoperfusion [hypotension, evidence of distal hypoperfusion (oliguria, increased creatinine, necrotizing enterocolitis, intraventricular hemorrhage or increased middle cerebral artery resistance, persistent metabolic acidosis)]; increased ventilatory parameters; and radiological evidence of cardiomegaly, pulmonary edema, or pulmonary hemorrhage. For the diagnosis of hs-PDA, ductal size, presence of any other echocardiographic alteration, and at least one clinical manifestation were considered.

The demographic data of the preterm population was: gestational age established by the date of last maternal menstrual period and/or Ballard assessment performed before 48 hours by neonatologist; route of delivery; history of fetal lung maturation, considering as complete treatment two doses of betamethasone each 24 hours apart, incomplete maturation (with only one dose of treatment), or no maturation (not receiving betamethasone); APGAR score at 5 min of life; and postnatal age at the beginning of treatment with paracetamol.

At the beginning and the end of pharmacological treatment, the following laboratory tests were performed: serum creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin to evaluate liver function; blood count to evaluate platelet count and hemoglobin, and cranial ultrasound to rule out ventricular hemorrhage, in order to detect possible adverse effects related to the administration of paracetamol.

Other variables analyzed were postnatal age at first echocardiography, PDA caliber, type of mechanical ventilation used during treatment with paracetamol, and presence of morbidities such as pulmonary hemorrhage, severe intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP) (according to the international classification of ROP); early or late neonatal sepsis, acute kidney injury (AKI) defined as an acute alteration of renal function according to the KDIGO classification in newborns (increase in plasma creatinine > 0.3 mg/dl of basal creatinine or oliguria < 0.5 ml/kg/h)[17], bronchopulmonary dysplasia (BPD) using the NIH 2001 classification, and periventricular leukomalacia (PVL). The different morbidities were evaluated in relation to the closure or not of the PDA with the first course of treatment with paracetamol.

Treatment failure with the first course of this drug was defined as the failure of closure of the hs-PDA, as evidenced by echocardiography. After the failure of two courses of complete treatment with paracetamol, surgical closure was considered.

The data were collected from the clinical records in a data table designed by the authors, and tabulated in Microsoft Excel version 365.

Statistical analysis

Absolute and relative frequencies were calculated for each categorical variable; for continuous variables, measures of central tendency and dispersion were used; whenever the distributional assumption of normality was met, the t-Student test was applied for the comparison of two paired samples. For those variables that did not meet the normality assumption, the Wilcoxon test was performed and the median and quartiles were calculated, and the median and interquartile range were presented. The chi-square test and Fisher's exact test were used to cross-check categorical variables.

To predict the probability of ductal closure with the first course of paracetamol, the logistic regression model with binomial link function was used, with the variables ductal diameter and gestational age being significant for the model.

A p-value of < 0.05 was considered significant. Data analysis was performed with Python statistical software version 3.1 and R-study version 4.2.1.

The study was approved by the Scientific Ethics Committee of the Concepción Health Service, Chile, Code CEC-SSC: 22-06-20. Informed consent was requested from one of the parents and a waiver of consent was requested for those who could not be contacted.

Results

98 VLBW preterm newborns were studied, of which 36 were excluded (figure 1). The mean weight and gestational age ± SD were 1,094 ± 257 g and 27.9 ± 2.1 weeks, respectively. 75.8% (47/62) were born by cesarean section, with no sex predominance (table 1).

The mean ductal diameter ± SD pre-treatment was 2.16 ± 0.52 mm. The postnatal age at first ultrasound and initiation of treatment was on average 2.4 days of life (table 1).

The most frequent morbidities were BPD (64.5%), late sepsis (45.2%), and IVH of any type (30.7%) (table 1).

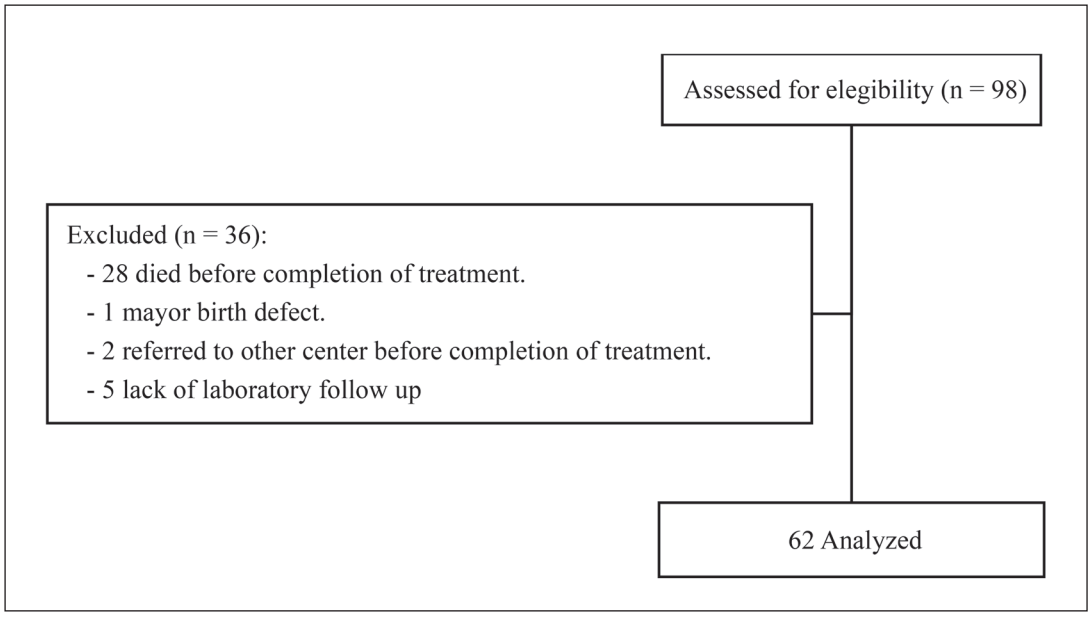

Figure 1. Selection diagram.

Table 1. Demographic background and morbidities of 62 very low birth weight newborn with hs-PDA treated with paracetamol

Birth weight, grams $\bar{x}$ ± SD	1094 ± 257
Gestational age, weeks $\bar{x}$ ± SD	27.9 ± 2.1
Gender, male (%)	32 (51.6)
Delivery, c-section n (%)	47 (75.8)
Complete pulmonary maturity, n (%)	45 (72.6)
Apgar 5 minutes, median (range)	8 (1-9)
Age at diagnosis (days) $\bar{x}$ ± SD	2.4 ± 0.7
Age at treatment initiation (days) $\bar{x}$ ± SD	2.4 ± 0.7
Ductal size, millimeters $\bar{x}$ ± SD	2.2 ± 0.5
Morbidities:	
Early onset sepsis, n (%)	6 (9.7)
Late onset sepsis, n (%)	28 (45.2)
Intraventricular hemorrhage, n (%)	19 (30.7)
Pulmonary hemorrhage, n (%)	7 (11.3)
Acute kidney injury, n (%)	10 (16.1)
Necrotizing enterocolitis, n (%)	9 (14.5)
Bronchopulmonary dysplasia, n (%)	40 (64.5)
Moderate/Severe Bronchopulmonary dysplasia, n (%)	12 (19.4)
Retinopathy of prematurity, n (%)	16 (25.8)
Periventricular leukomalacia, n (%)	5 (8.1)

SD: Standard deviation, $\bar{x}$: mean

The ductal closure rate with the first course of paracetamol was 69.4% (43/62), increasing to 87.1% (54/62) with the second course of treatment. Surgical closure was required in 9.7% of newborns (6/62) (table 2). In 2 newborns, the ductus did not close with a second course of paracetamol but significantly decreased in size, thus surgical closure was not necessary.

When analyzing the results of ductal closure by subgroups according to gestational age ≥ 28 weeks and < 28 weeks, and birth weight ≥ 1,000 g or < 1,000 g, there was a greater response to treatment with paracetamol in newborns with gestational age ≥ 28 weeks, which was statistically significant (p = 0.015) (table 3).

Figure 2 shows that the probability of closure with a first course of paracetamol increases by 81% for each week increase in gestational age (odds ratio (OR) 1.81; 95% confidence interval (CI) = 1.25-2.62). Similarly, the effect of ductus size on the probability of closure with a first course decreases by 79% for every 1 mm increase in PDA size (OR 0.21; 95%CI = 0.06-0.70). It

Table 2. Results with prolonged treatment with paracetamol in very low birth weight newborn

Closure with first paracetamol course n (%)	43 (69.4)
Closure with second paracetamol course, n (%)	11 (17.7)
Surgical closure, n (%)	6 (9.7)

Table 3. Results with prolonged paracetamol treatment according to gestational age and weight

	Closure with first paracetamol course, n (%)	Closure with second paracetamol course, n (%)	Surgical closure, n (%)	p
< 28 weeks	11 (17.8)	5 (8.1)	5 (8.1)	0.015*
≥ 28 weeks	32 (51.6)	6 (9.6)	1 (1.6)	
< 1.000 g	14 (22.6)	3 (4.8)	4 (6.5)	0.218
≥ 1.000 g	29 (46.8)	8 (12.9)	2 (3.2)	

Chi-square test. *p < 0.05.

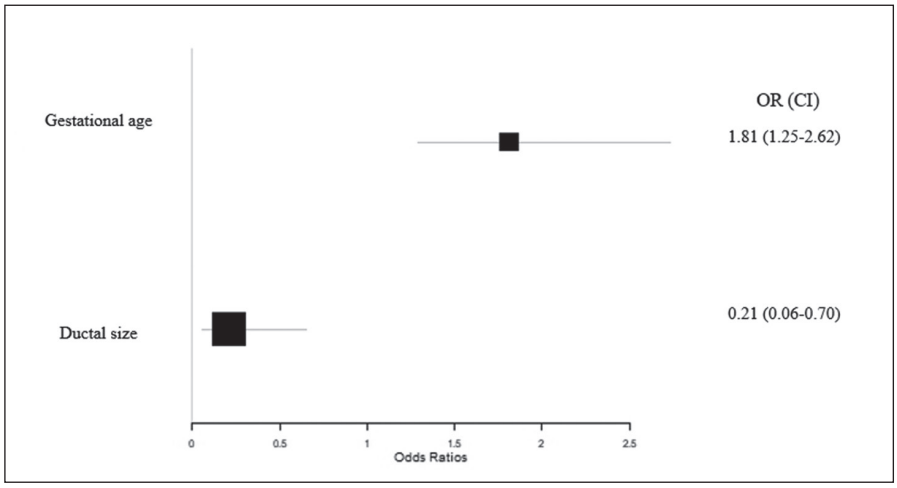

Figure 2. Probability of closure of patent ductus arteriosus (PDA) with first course of intravenous paracetamol according to gestational age in weeks and ductal size in millimeters. OR: Odds ratio, CI: Confidence interval.

should be noted that other variables were considered such as birth weight and ventilatory support, which were not significant for the logistic model used.

Regarding the morbidities of VLBW preterm newborns with hs-PDA that had closure versus those that did not with the first course of paracetamol, it was observed that those newborns that did not present late sepsis had closure in a higher proportion than those that did (p = 0.001). In addition, it was observed that in the total number of preterm newborns analyzed, whose hs-PDA closed with the first course of paracetamol, there was a significant decrease in the incidence of stage II and III ROP (p = 0.002) and AKI (p = 0.006). In the group of preterm newborns under 28 weeks of gestational age whose hs-PDA closed with the first course of paracetamol, a significant decrease in AKI was also observed (p = 0.027). In the rest of the neonatal morbidities analyzed, there were no significant differences (table 4).

Likewise, it was observed that the newborns with noninvasive ventilatory support had closure in a higher proportion than those with invasive ventilatory support (table 4).

Regarding the laboratory tests evaluated at the end of treatment with paracetamol, a significant increase in platelet count (p = 0.001) and a decrease in serum creatinine (p = 0.001) were observed (table 5).

Discussion

The use of paracetamol in the closure of hs-PDA in preterm newborns has been studied for more than a decade. Initially, it was used as an alternative to indomethacin or ibuprofen in those cases in which the use of these drugs was contraindicated[11,18]. In 2011, C. Hammerman et al.[11], published the first report on the use of paracetamol for PDA closure in 5 preterm newborns ≤ 32 weeks gestational age in whom the use of ibuprofen and indomethacin was contraindicated. Administration of paracetamol at 15 mg/kg dose every 6 hours (60 mg/kg/day) was reported to be effective for PDA closure. After that publication, several studies have been reported, demonstrating a satisfactory percentage of ductal closure with the administration of paracetamol, when compared mainly with ibuprofen.

Table 4. Respiratory support and morbidities in VLBWNB with hs-PDA closure with first paracetamol course vs non respondants

	< 28 weeks (n = 23)			< 32 weeks (n = 62)		
	Closure n = 11 (%)	No closure n = 12 (%)	p	Closure n = 43 (%)	No closure n = 19 (%)	p
Respiratory support Non invasive Invasive	 2 (8.7) 9 (39.1)	 1 (4.3) 11 (47.8)	 0.590	 24 (38.7) 19 (30.6)	 3 (4.8) 16 (25.8)	 0.007*
Late onset sepsis	1 (4.3)	3 (13.0)	0.590	3 (4.8)	3 (4.8)	0.359
No late onset sepsis	4 (17.4)	2 (8.7)	0.371	30 (48.4)	4 (6.5)	0.001*
Pulmonary hemorrhage	1 (4.3)	2 (8.7)	1.000	4 (6.5)	3 (4.8)	0.665
Intraventricular hemorrhage Stage III-IV	8 (34.8)	10 43.5)	0.317	4 (6.5)	1 (1.6)	1.000
Acute kidney injury	1 (4.3)	7 (30.4)	0.027*	3 (4.8)	7 (11.3)	0.006*
Retinopathy of prematurity ROP stages II y III	4 (17.4)	9 (39.1)	0.100	4 (6.5)	9 (14.5)	0.002*
Bronchopulmonary dysplasia Moderate/Severe	4 (17.4)	6 (26.1)	0.680	6 (9.7)	6 (9.7)	0.162
Periventricular Leukomalacia	2 (8.7)	2 (8.7)	1.000	3 (4.8)	2 (3.2)	0.638

Chi square test/Fisher's exact test / *= $p < 0.05$.

Table 5. Laboratory tests performed before and after treatment with paracetamol

Tests	Pre-treatment	Post-treatment Mean + SD	p
Blood ureic nitrogen (mg/dL)	18.9 ± 10.5	13.4 ± 8.5	0.990
Total serum bilirubin (mg/dL)	7.5 ± 2.8	3.5 ± 2.8	0.990
Platelet count (mcL)	209.225 ± 70.190	290.440 ± 111.393	0.001*
Hemoglobin (g/dL)	15.0 ± 2.2	11.7 ± 1.6	0.990
		Median ± Interquartile range	
Serum creatinine (mg/dL)	0.7 ± 0.2	0.5 ± 0.3	0.001*
Serum alanine aminotransferase (mg/dL)	8.0 ± 1.8	9.5 ± 3.0	0.119
Serum aspartate aminotransferase (mg/dL)	21 ± 23.0	21± 8.0	0.538

Student's t-test and Wilcoxon ranks / *= $p < 0.05$.

Most of these studies used a dose of 15 mg/kg for 3 days[12, 19-21].

To the best of our knowledge, this study is the first using 6 consecutive days of intravenous paracetamol. In India in 2015, Dash et al.[22] published a prospective comparative study between oral paracetamol and intravenous indomethacin using a paracetamol dose of 15 mg/kg every 6 hours for 7 days in 36 preterm newborns weighing < 1,500 g, observing a primary closure rate of 100%. Subsequently, Härkin et al.[14] reported a prospective study of 48 VLBW preterm newborns using prophylactic intravenous paracetamol (first 24 hours of life) in one group and placebo in the other (n = 23/25). The initial dose was 20 mg/kg followed by 7.5 mg/kg every 6 hours for 4 days, reporting that the group that received prophylactic paracetamol closed earlier than the group that received placebo. The EPAR study[23] in 58 preterm newborns < 29 weeks of gestation used intravenous paracetamol for 5 days achieving a primary ductal closure of 69%. In these last 2 clinical trials, the dose and duration of treatment were lower than that used in our study since the maintenance dose of paracetamol was 7.5 mg/kg every 6 hours.

The rate of primary ductal closure in this study (69.4%) is similar to that reported by Al-lawama et al. (69%), by Yang et al. (70%), and by the EPAR study (69%)[23-25]. However, in other publications with populations similar to ours, the reported rate is higher, achieving ductal closure in up to 95% of cases[20,26,27]. It should be noted that in these studies oral paracetamol was used, and the higher percentage of ductal closure may be due to more stable drug levels when administered by this route[28].

In those preterm newborns whose hs-PDA did not close with the first course of paracetamol, a second course of this drug was administered, increasing the percentage of ductal closure, and decreasing the risk of surgical closure of the ductus. The increase in ductal closure with the second course of treatment has also been observed in other clinical studies[15,20,29].

A multivariate logistic model showed that the lower the gestational age and the larger the ductal diameter, the lower the possibility of closure. This result agrees with that published by Vaidya et al., who observed that newborns with gestational age at birth >26 weeks had a greater probability of successful ductal closure with paracetamol (RR = 1.92; 95%CI = 1.20-3.09), as did those with a ductal size < 2 mm (RR = 1.82; 95%CI = 1.11-2.98)[21].

Similarly, when comparing newborns < 28 weeks with those ≥ 28 weeks, it was found that newborns with a lower gestational age had a significantly lower rate of ductal closure, which is consistent with other clinical experiences[21,30].

Likewise, when comparing newborns weighing < 1,000 g with those > 1,000 g treated with paracetamol, it was found that newborns weighing < 1,000 g had a lower rate of ductal closure with the first course of paracetamol (22.6% vs. 46.8%). These findings coincide with the results of Murphy et al.[29], who evaluated 15 newborns with an average weight of 810 g, whose ductus did not close after treatment with paracetamol, and in parallel, echocardiographic evaluation showed minimal changes in ductal size before and after paracetamol administration. These observations have also been reported by other researchers[21,30].

This study showed a higher percentage of hs-PDA closure in those preterm newborns who were on non-invasive ventilatory support, possibly due to a lesser severity of their respiratory pathology. In the study by Clyman et al.[31], it was observed that newborns on prolonged invasive mechanical ventilation (more than 10 days), and who had a longer exposure time to PDA, were at a significantly higher risk of presenting BPD in the future. In our study, there was no significant difference in the incidence of moderate/severe BPD between those newborns whose PDA closed with a first course of paracetamol versus those who did not close. However, an increased incidence of overall BPD was observed in the population studied when compared with previous data from our service (64.5% vs. 27.2%). However, these data include the total population of VLBW preterm newborns and not only newborns with hs-PDA, as is the case of our study[32]. Recent publications on the use of paracetamol in the treatment of PDA in VLBW preterm newborns have highlighted a potential risk of lung damage with paracetamol therapy, which would be evidenced by an increase in the BPD incidence[33-35].

On the other hand, an increase in hs-PDA closure was observed in newborns who were not suffering from late sepsis, a clinical finding that has been observed previously. In the study of Gonzalez et al.[36], it was shown that newborns with an infection presented a decrease in ductal closure or reopening of the ductal closure, possibly due to increased levels of prostaglandins and tumor necrosis factor-alpha, which is observed in newborns with sepsis.

In addition, a decrease in the incidence of AKI and ROP was observed in those who closed with the first course of paracetamol. This observation is possibly related to a shorter exposure time to hs-PDA and to a higher gestational age at the time of diagnosis so that these premature newborns had a better response to treatment. None of the studies published to date have shown that pharmacological closure of PDA protects against ROP or AKI in preterm newborns[11,14,19,23,37].

Paracetamol has a predominantly hepatic metabolism, so its administration can be potentially harmful to the liver[9]. However, in several published studies, no hepatic alteration has been observed, mainly evaluated through the measurement of transaminases in VLBW preterm newborns receiving treatment with this drug[15,20,22,26,37].

In this clinical trial, the laboratory tests evaluated in general did not show significant alterations at baseline or after prolonged use of intravenous paracetamol (6 days). However, serum creatinine showed a significant decrease when evaluated after 6 days of treatment. This decrease would be due to the drop in serum creatinine that usually occurs during the first week of life in the newborn as opposed to the value before treatment (first 72 hours postnatal) which normally reflects the value of maternal serum creatinine and tubular reabsorption[38]. The post-treatment tests were performed on average at 8.4 days postnatal life, corresponding, therefore, to the newborn's own serum creatinine. Regarding the rest of the tests analyzed, an increase in platelet count was observed at the end of 6 days of treatment, a value that is within normal ranges and that would not have any clinical implications. These results of the laboratory tests agree with other investigations in which no changes are observed before or af-

ter the administration of paracetamol[9,10,14,15,27]. Most of the previous studies used lower doses of paracetamol than the one used in this investigation.

When comparing the primary ductal closure of this study (69.4%) with the cohort previously evaluated in our center (unpublished observations), with only 3 days of treatment with paracetamol, there was about a 3% increase in the rate of ductal closure. This slight increase in ductal closure with prolonged treatment of 6 days would not justify extending the duration of treatment.

Among the weaknesses, this study, being a retrospective cohort, has some limitations. Control echocardiography was not performed on the third day of treatment, and the PDA could have closed before the control on the sixth day. In addition, some interventions that could influence or favor ductal reopening were not considered, such as the number and volume of transfusions indicated, which could be incorporated in new research, as well as the subsequent follow-up of these patients, at 18-24 months of life.

Among its strengths is the evaluation of the prolonged use of intravenous paracetamol for 6 consecutive days, which has not been previously evaluated in other investigations. Echocardiographic evaluations of PDA were performed throughout the study period by the same pediatric cardiologists, always using the same diagnostic criteria.

Conclusion

In VLBW preterm newborns with hs-PDA, prolonged treatment with intravenous paracetamol does not increase the rate of primary ductal closure with respect to the usual treatment of only 3 days. The increase in the number of days of paracetamol administration could mean an increase in lung injury, manifested as BPD. However, new randomized multicenter studies are needed to evaluate the possible role of this drug at the pulmonary level.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

References

1. Prescott S, Keim-Malpass J. Patent Ductus Arteriosus in the Preterm Infant: Diagnostic and Treatment Options. Adv Neonatal Care. 2017;17:10-8. doi: 10.1097/ANC.0000000000000340.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39:1890-900. doi: 10.1016/s0735-1097(02)01886-7.
3. Mitra S, McNamara PJ. Patent Ductus Arteriosus - Time for a definitive trial. Clin. Perinatol. 2020;47:617-39. doi: 10.1016/j.clp.2020.05.007.
4. Koch J, Hensley G, Roy L, et a. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics. 2006;117:1113-21. doi: 10.1542/peds.2005-1528.
5. Hamrick S, Sallmon H, Rose A, et al. Patent Ductus Arteriosus of the Preterm Infant. Pediatrics. 2020;146:e20201209. doi: 10.1542/peds.2020-1209.
6. Mitra S, Chan AK, Paes BA. Thrombosis and Hemostasis in Newborns (THIN) Group. The association of platelets with failed patent ductus arteriosus closure after a primary course of indomethacin or ibuprofen: A systematic review and meta-analysis. J Mater Fetal Neonatal Med. 2017;30:127-33. doi: 10.3109/14767058.2016.1163684.
7. Schmidt B, Roberts RS, Fanaroff A. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the trial of indomethacin prophylaxis in preterms (TIPP). J Pediatr. 2006;148:730-4. doi: 10.1016/j.jpeds.2006.01.047.
8. Zecca E, Romagnoli C, De Carolis MP, et al. Does Ibuprofen increase neonatal hyperbilirubinemia? Pediatrics. 2009;124:480-4. doi: 10.1542/peds.2008-2433.
9. King R, Colon M, Stanfel L, et al. Late Acetaminophen Therapy for Patent Ductus Arteriosus in the Preterm Neonate. J Pediatr Pharmacol Ther. 2020;25:507-13. doi: 10.5863/1551-6776-25.6.507.
10. Surak A, Jain A, Hyderi A. Different approaches for patent ductus arteriosus in premature infants using acetaminophen. World J Pediatr. 2022;18:243-50. doi: 10.1007/s12519-022-00526-4.
11. Hammerman C, Bin-Nun A, Markovitch E, et al. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. Pediatrics. 2011;128:e1618-1621. doi:10.1542/peds.201 1-0359.
12. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database Syst Rev. 2018;4:CD01006. doi: 10.1002/14651858.CD010061.pub3.
13. Terrin G, Conte F, Oncel MY, et al. Paracetamol for the treatment of patent ductus arteriosus in preterm neonates: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2016;101:F127-136. doi: 10.1136/archdischild-2014-307312.
14. Härkin P, Härma A, Aikio O, et al. Paracetamol Accelerates Closure of the Ductus Arteriosus after Premature Birth: A Randomized Trial. J Pediatr. 2016;177:72-7. doi: 10.1016/j.jpeds.2016.04.066.
15. Dani C, Lista G, Bianchi S, et al. Intravenous paracetamol in comparison with ibuprofen for the treatment of patent ductus arteriosus in preterm infants: a randomized controlled trial; Eu J Pediatr. 2021;180:807-16. doi: 10.1007/s00431-020-03780-8
16. McNamara PJ, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. Arch Dis Child Fetal Neonatal. 2007;92:F424-F427. doi: 10.1136/adc.2007.118117.
17. Jetton JG, Askenazi DJ. Acute kidney injury in the neonate. Clin Perinatol. 2014;4:487-502. doi: 10.1016/j.clp.2014.05.001.
18. Oncel MY, Yurttutan S, Uras N, et al. An alternative drug (paracetamol) in the management of patent ductus arteriosus in ibuprofen-resistant or contraindicated preterm infants. Arch Dis Child Fetal Neonatal Ed. 2013;98:F94. doi: 10.1136/archdischild-2012-302044.
19. Xiao Y, Liu H, Hu R, et al. Efficacy and Safety of Paracetamol for Patent Ductus Arteriosus Closure in Preterm Infants: An Updated Systematic Review and Meta-Analysis. Front Pediatr. 2020;7:568-74. doi: 10.3389/fped.2019.00568
20. El-Mashad AE, El-Mahdy H, El Amrousy D, et al. Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates. Eur J Pediatr. 2017;176:233-40. doi: 10.1007/s00431-016-2830-7.
21. Vaidya R, Knee A, Paris Y, et al. Predictors of successful patent ductus arteriosus closure with acetaminophen in preterm infants. J Perinatol. 2021;41:998-1006. doi: 10.1038/s41372-020-00803-y.
22. Dash SK, Kabra NS, Avasthi BS, et al. Enteral paracetamol or Intravenous Indomethacin for Closure of Patent Ductus Arteriosus in Preterm Neonates: A Randomized Controlled Trial. Indian Pediatrics. 2015;52:573-8. doi: 10.1007/s13312-015-0677-z.
23. Schindler T, Smyth J, Bolisetty S, et al. Early PARacetamol (EPAR) trial: a study protocol for a randomised controlled trial of early paracetamol to promote closure of the ductus arteriosus in preterm infants. BMJ Open. 2019;30:e031428. doi: 10.1136/bmjopen-2019-031428.
24. Al-Lawama M, Alammori I, Abdelghani T, et al. Oral paracetamol versus oral ibuprofen for treatment of patent ductus arteriosus, Journal of International Medical Research. 2017;46:1-8. doi: 10.1177/0300060517722698.
25. Yang B, Gao X, Ren Y, et al. Oral paracetamol vs. oral ibuprofen in the treatment of symptomatic patent ductus arteriosus in premature infants: a randomized controlled trial. Exp Ther Med. 2016;12:2531-6. doi: 10.3892/etm.2016.3676.
26. Kumar A, Gosavi RS, Sundaram V, et al. Oral paracetamol vs oral ibuprofen in patent ductus arteriosus: a randomized, controlled, noninferiority trial. J Pediatr. 2020;222:79-84. doi: 10.1016/j.jpeds.2020.01.058.
27. El-Farrash RA, El Shimy MS, El-Sakka AS, et al. Efficacy and safety of oral paracetamol versus oral ibuprofen for closure of patent ductus arteriosus in preterm infants: a randomized controlled trial. J Matern Fetal Neonatal Med. 2019;32:3647-54. doi: 10.1080/14767058.2018.1470235.
28. Gover A, Levy PT, Rotschild A, et al. Oral versus intravenous paracetamol for patent ductus arteriosus closure in preterm infants. Pediatr Res. 2022;92:1146-52. doi: 10.1038/s41390-022-01944-w.
29. Murphy C, Bussmann N, Staunton D, et al. The effect of patent ductus arteriosus treatment with paracetamol on pulmonary vascular resistance. J Perinatol. 2022;42:1697-8. doi: 10.1038/s41372-022-01410-9.
30. Clyman RI, Liebowitz M, Kaempf J, et al. PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age. J Pediatr. 2019;205:41-48. doi: 10.1016/j.jpeds.2018.09.012.
31. Clyman RI, Kaempf J, Liebowitz M, et al. PDA-TOLERATE Trial Investigators. Prolonged Tracheal Intubation and the Association Between Patent Ductus Arteriosus and Bronchopulmonary Dysplasia: A Secondary Analysis of the PDA-TOLERATE trial. J Pediatr. 2021;229:283-8. doi: 10.1016/j.jpeds.2020.09.047.
32. Bancalari A. Actualización en Presentación y Patogénesis de la Displasia Broncopulmonar. Rev Chil Pediatr. 2009;80:213-24. doi: 10.4067/S0370-41062009000300002.

33. Wright C, McCulley D, Mitra S, Jensen Erik. Acetaminophen for the patent ductus arteriosus: has safety been adequately demonstrated?. J Perinatol. 2023;43:1230-7. doi: 10.1038/s41372-023-01697-2.
34. Wright CJ. Acetaminophen and the Developing Lung: Could There Be Lifelong Consequences? J Pediatr. 2021;235:264-76. doi: 10.1016/j.jpeds.2021.02.026.
35. McCulley DJ, Jensen EA, Sucre JMS, et al. Racing against time: leveraging preclinical models to understand pulmonary susceptibility to perinatal acetaminophen exposures. Am J Physiol Lung Cell Mol Physiol. 2022;323:L1-L13. doi: 10.1152/ajplung.00080.2022.
36. Gonzalez A, Sosenko IR, Chandar J, et al. Influence of infection on patent ductus arteriosus and chronic lung disease in premature infants weighing 1000 grams or less. J Pediatr. 1996;128:470-8. doi: 10.1016/s0022-3476(96)70356-6.
37. Su BH, Lin HY, Chiu HY, et al. Therapeutic strategy of patent ductus arteriosus in extremely preterm infants. Pediatr Neonatol. 2020;61:133-41. doi: 10.1016/j.pedneo.2019.10.002.
38. Justin T. Kastl. Renal function in the fetus and neonate – the creatinine enigma, Semin Fetal Neonatal Med. 2017;22:83-9. doi: 10.1016/j.siny.2016.12.002.